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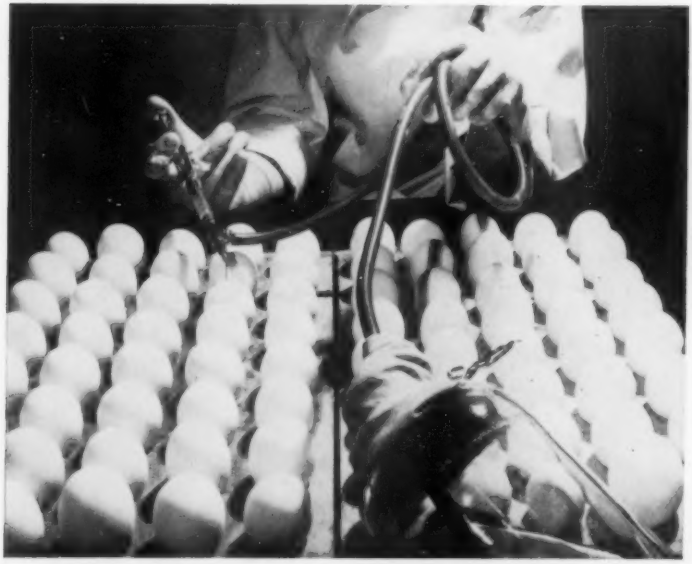

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AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825

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EDITORIAL

THE GENERIC NAME PITFALL

EVERY so often, there is renewed effort sometimes bordering on agitation to promote the use of generic names. In recent weeks, such efforts have been intensified largely, we presume, as a means of offsetting some of the criticism which has been directed against the pharmaceutical industry by the Kefauver hearings. We do not at this time wish to comment on the real reason behind Senator Kefauver's "investigation." This, we shall defer until a future time since it is a subject in itself. We do wish, however, to draw attention to some of the pitfalls which are overlooked even by well-intentioned people in their advocacy of the use of generic names and in their suggestion that physicians grant blanket approval to pharmacists to dispense a generic equivalent when a brand name is prescribed.

First, we shall take up the problem of generic names. It would be difficult to imagine the utter chaos which would result if, let us say, for the next week all prescriptions written in the United States were written using generic names. Physicians themselves are totally unfamiliar with these names and pharmacists, we suspect, do not know one out of ten. By no conceivable process of professional education could this situation be remedied. Generic names by their very nature are extremely difficult to remember—sometimes, we suspect, almost by intent. Even when those who are given the task of coining generic names do it with complete objectivity and follow all of the standard rules for nomenclature such as those promulgated by the World Health Organization, they come up with names which are real tongue-twisters and almost impossible for the average practitioner to spell. With just a little imagination, one can picture just what might happen when such names, improperly spelled to start with, and illegibly written besides, were placed on prescriptions. The average pharmacist would be lucky indeed if he could figure out the physician's intent on half the prescriptions which he received. We presume that this difficulty might in time be remedied with an intensive educational

campaign directed at both the medical and pharmaceutical professions but, until such a campaign bore fruit, we could expect all sorts of tragic errors—some of colossal magnitude.

Another aspect of the situation which deserves more attention than it has received is just how often a bona fide, high quality pharmaceutical is available except under its brand name. There are hundreds of important prescription products that are not commercially available except under their brand names unless it be some counterfeit of doubtful identity and even more doubtful quality and purity. This same situation exists in almost all cases except with a very few drugs which are relatively old and which are manufactured by several companies of good reputation.

The most serious aspect in connection with the widespread use of generic names and efforts to make the use of generic names popular is the encouragement it would give to some of the most unprincipled duplicators and counterfeiters of pharmaceuticals on the American scene. These undercover companies have always been with us and the inroads which they have made on the sales of pharmaceuticals by our legitimate and ethical companies have at times been staggering. Almost invariably, it is found that these companies operate without proper manufacturing supervision and control and that they are constantly in trouble with the Food and Drug Administration or some state agency having similar responsibilities. These companies originate solely because of the cupidity of their owners who depend upon equal cupidity and greed on the part of certain pharmacists. Their existence and their modus operandi are so well-known in pharmaceutical circles that they need not be discussed here. Some of our finest pharmaceutical companies are constantly engaged in shaking off these leeches who have never done a single thing to advance or improve pharmacy, have never supported the slightest bit of research, do not employ competent help, and have not the slightest sense of responsibility for their actions.

If the various proposals to extend the use of generic names should be seriously accepted by the professions and some effort made to implement these proposals, we can expect a mushrooming of these submarginal operators with the eventual result that we shall return to those days of chaos when drugs rarely met prescribed standards and adulteration was the rule rather than the exception. Public confidence in the drug industry might well then be completely shaken.

This could spell the end of private initiative in the drug field and bring us all under a regimented system of state medicine.

We in pharmacy in the United States have reason to be proud of our accomplishments for they are unmatched in the world. Before those who advocate some departure from our present system are taken seriously, it would be well for us to think carefully concerning what might be the eventual result of the innovations they suggest. For the first time in our history, the drug industry is being subjected to public attacks by fakirs and charlatans. It is time for us to stand steadfast by our guns and on the solid record of our achievements and not seek public acclaim on the basis of proposals which, while they sound good on the surface, may contain in them the seeds of the eventual destruction of our entire system of medical care.

L. F. Tice

EVALUATION OF DIURETIC AGENTS *

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Part I

By John E. Baer

A DIURETIC is an agent that will increase the excretion of urine and the components that are found in urine. Those agents which simply increase renal blood flow and glomerular filtration rate may increase urine formation as a result of improved renal hemodynamics, but they are not diuretic agents in the sense of promoting the excretion of salt or water by their local action in the kidney (1).

Clinically, diuretic agents are used principally in conditions where edema or swelling or puffiness of the tissues due to fluid retention has occurred. Edema or fluid retention may be associated with pathological states such as congestive failure, ascites, edemas and toxemias of pregnancy, dependent or localized edema or may be iatrogenically-induced during therapy with certain steroid hormones.

In light of the definition and clinical utility of diuretic agents, we may consider various possibilities for their evaluation: (a) We can evaluate these agents in terms of the mechanisms by which they act, or through which they act, in the kidney. (b) We can try to evaluate these agents in conditions which simulate clinical pathological conditions. (c) We can use a rather arbitrary animal test which we hope ultimately will correlate with the effect in man. (d) We can perform our evaluation in terms of the physiology of the organ involved, i.e.—the kidney. In the following discussion, we shall illustrate some of these types of evaluation procedures.

I. In order to get an indication of the types of mechanisms which might be involved, and against which one could test the action of potential diuretic agents, I would like to review briefly some of the principal classes of diuretic agents.

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* Presented at the Seminar on *Current Methods of Drug Evaluation*, December 1958, Philadelphia College of Pharmacy and Science, Philadelphia 4, Pennsylvania.

A. *Osmotic diuretic agents:* Urea, mannitol, and other agents which themselves are not reabsorbed by the kidney. By virtue of passing through the kidney unreabsorbed, these agents carry with them a certain amount of water and, consequently, a certain amount of the electrolytes that are present in the tubular fluid.

B. *Xanthine diuretic agents:* Caffeine, theophylline, theobromine, aminophylline. In addition to a weak effect on increasing glomerular filtration rate, these agents may cause an inhibition of the reabsorption of sodium and/or chloride ion. They do not promote imbalance as far as acidosis-alkalosis is concerned. They are not very potent.

C. *Amino-uracils and triazines:* Aminometradine (Mictine ®), amisometradine (Rolicton ®), chlorazanil (Daquin ®). These diuretics tend to inhibit the tubular reabsorption of sodium and chloride ions, thus causing an enhanced excretion of sodium chloride and water.

D. *Mercurial diuretic agents:* Chlormerodin (Neohydrin ®), meralluride (Mercuhyrin ®), mersalyl (Salyrgan ®), etc. Mercury ions or the organo-mercurial molecule itself may find receptor sites on sulfhydryl or carboxamido groups in an enzyme which is responsible for sodium or chloride transport and, thereby, impede the activity of this enzyme within the kidney (2, 3). With this particular category of compound, one may approach a more fundamental enzymatic point of view and consider, at least in theory, the idea of using an isolated enzyme system for evaluating potential mercurial diuretics.

E. *Carbonic anhydrase inhibitors:* Acetazolamide (Diamox ®), dichlorphenamide (Daranide ®), ethoxzolamide (Cardrase ®). These diuretics characteristically contain a sulfonamide ($-SO_2NH_2$) grouping and are potent inhibitors *in vitro* of the enzyme carbonic anhydrase. Explanations and experimental justifications have been proposed for carbonic anhydrase inhibition as the mode of diuretic action of these agents (4). They cause considerable excretion of bicarbonate resulting in a metabolic acidosis.

F. *Chlorothiazide and related saluretic agents:* Chlorothiazide (Diuril ®), hydrochlorothiazide (Hydrodiuril ®), flumethazide (Ademol ®), hydroflumethazide (Saluron ®). These agents are also *in vitro* carbonic anhydrase inhibitors. They cause the excretion of

nearly equivalent quantities of sodium and chloride, so that no metabolic acidosis results from their repeated administration (5).

II. The variety of modes of action that are implicit in the foregoing review suggest that it would not be easy to find a simple test for all possible kinds of diuretic activity.

A. Let us first consider two possible types of *in vitro* tests. As far as the mercurials are concerned, there is good reason to suppose that an enzyme system (or systems) may be implicated because such activity has been described for a large number of organo-mercurial agents of varying structure. There have been attempts to correlate the activity of mercurial agents with the solubility of the agent in water (Breyer, 1939), with the solubility in alkali (Fourneau, 1931), the ionizability either of the organo-mercurial to free mercury or to a molecule that will react with sulfhydryl groups (Rowland, 1952).

The renal enzyme has not been characterized, isolated, or exactly located. Several microhistological studies have been performed in an attempt to equate the site of succinic dehydrogenase with the location of mercurial atoms after the administration of organo-mercurials in animals. There has seemed to be some concentration of mercurial diuretic in the distal end of the proximal tubule as well as in the distal tubules and in the collecting ducts. These observations have been made largely with higher than therapeutic doses of the mercurials and one wonders whether these histopathologic studies may represent something other than actual diuretic activity. One worker has stated that there is a definite and definitive histochemical distinction between the site of action of mercurials and succinic dehydrogenase sites in the kidney (6). Others have held exactly the opposite view (7). Such an *in vitro* system, however, remains an attractive possibility as a screening test for this type of agent.

Carbonic anhydrase is an enzyme for which *in vitro* methods are available to study inhibitors thereof as possible diuretic agents. This enzyme which is present in the gastric mucosa, the kidney, the red blood cells, and the brain accelerates the rate at which carbon dioxide can be dissolved in aqueous solutions. This process, in the absence of an enzyme, will come to equilibrium in a few minutes but, in the presence of the enzyme carbonic anhydrase, solution occurs almost instantaneously. The enzyme is a well-characterized material which is now commercially available. *In vitro* systems have been described

by numerous workers. The method of Philpot (1936) is one which utilizes the change in pH and a colorimetric endpoint and is a very easy one to set up in the laboratory. This type of a system was used by Miller (8) and others in the selection of acetazolamide from among a group of compounds on the basis of potency as an inhibitor of carbonic anhydrase.

There are factors other than the inherent *in vitro* activity of carbonic anhydrase which are important in the qualitative as well as quantitative distinction between agents in class E and those in class F, even though they all have a measure of inhibitory activity against carbonic anhydrase. Comparing the *in vitro* activity of acetazolamide, chlorothiazide, and sulfanilamide (Fig. 1), one sees that acetazolamide is some 20 times as potent as chlorothiazide, which in turn is some 15 times as potent as sulfanilamide *in vitro* as an inhibitor of carbonic anhydrase. However, the *in vivo* diuretic activity of chlorothiazide is greater than either acetazolamide or sulfanilamide. The more potent diuretic, hydrochlorothiazide, is as weak an inhibitor of carbonic anhydrase as sulfanilamide.

Even if the enzyme system which is known to be involved in the action of the drug is well-characterized and an *in vitro* study is made, other factors inevitably enter as one translates from an *in vitro* to an *in vivo* system. Among these factors which are obvious are oral absorption of the drug, its distribution among various tissues, degradation of the drug by the liver and other tissues of the body, the rate and mode of excretion of the substance, and other aspects. Thus, biochemical systems other than the one examined *in vitro* may, in fact, become of considerable importance.

B. *In vitro* tests may have some advantage in the preliminary evaluation of many substances since they may be performed at a relatively rapid rate. They must be followed by studies in living animals. The species selected, of course, for any evaluation should resemble man as closely as possible. It should be remembered that no animal resembles an edematous man exactly; that is, one who is in need of a diuretic agent. In fact, normal man does not exactly resemble the edematous patient so that the final test of diuretic activity and therapeutic utility is dependent upon clinical evaluation for effectiveness as well as a critical appraisal of possible toxic side-effects.

Attempts to simulate congestive failure or produce edema in animals have not led to useful evaluation procedures. Herken (9)

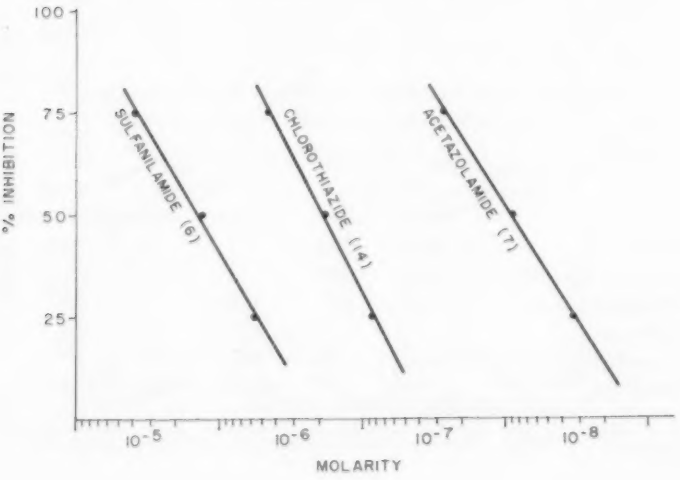
found that, upon water-loading, older rats became edematous and did not respond well to diuretics; whereas, young rats responded to water-loading with spontaneous diuresis. Development of ascites in dogs by constriction of the vena cava (10, 11) is a procedure that requires considerable skill. The administration of large amounts of steroids and salt may lead to edema and weight gain in dogs, but the edema may accumulate only very slowly.

The use of newer diuretics in hypertension suggests the use of experimental hypertensive animals as subjects for evaluation of the saluretic agents. To date, no satisfactory procedure has been reported.

C. For *in vivo* studies on the evaluation of diuretic agents in non-edematous animals, numerous species—mice, rabbits, cats, rats, dogs—have been used. The rat and the dog have been used most extensively. The first work by J. H. Burn on the use of the rat *in vivo* for diuretic testing signalled the beginning of systematic work

FIG. 1.

COMPARATIVE IN VITRO CARBONIC ANHYDRASE INHIBITING ACTIVITY OF SULFANILAMIDE, CHLOROTHIAZIDE, AND ACETAZOLAMIDE



in this area and was followed by the classical paper of Lipschitz *et al.* (12) in 1943.

Fourneau used rabbits for studying diuretics, and this species has been used occasionally for this purpose. There are certain practical objections in the difficulty of collecting urine from these creatures and the general unpredictability of their response. Cushney's comment on theophylline, "It is of marked diuretic action in the rabbit, moderate action in man, very slight in the dog, and no action in the cat," suggests that it is not always possible to extend observations in one species to predictions in another.

Lipschitz *et al.* (12) established a method of using male rats weighing between 140 and 240 grams, fasted and deprived of water for 18 hours. They were divided into five groups of eight rats, one group serving as a control and the other groups receiving two doses of each drug (or four doses of a single drug if one was trying to "range find" on a new drug). The control rats received 25 ml./Kg. of normal saline orally and the others received drug in the same total volume. All solutions were maintained at room temperature. The eight rats in each group were placed in two cages connected with a U-tube so that the urine from all eight rats was collected together. Urine was collected for five hours; at the end of five hours, the bladder was

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FIG. 2.*

COMPARISON OF DIURETIC ACTIVITIES FROM THE DOSE—ACTION CURVES AND IN HUMAN THERAPY

	Approx. Dose mg./kg.		*Relative Activity*		*Ratio*
	Human	*Rat*	*Human*	*Rat*	*Rat/Human*
Urea	600	1500	1	1	2.5
Ammon. Chloride	300	500	2	2.7	1.6
Theobromine	9	200	150	7	20
Caffeine	1.5	50	625	32	50
Theophylline	3	30	480	115	10
Mersalyl	1.6	35	1250	400	5

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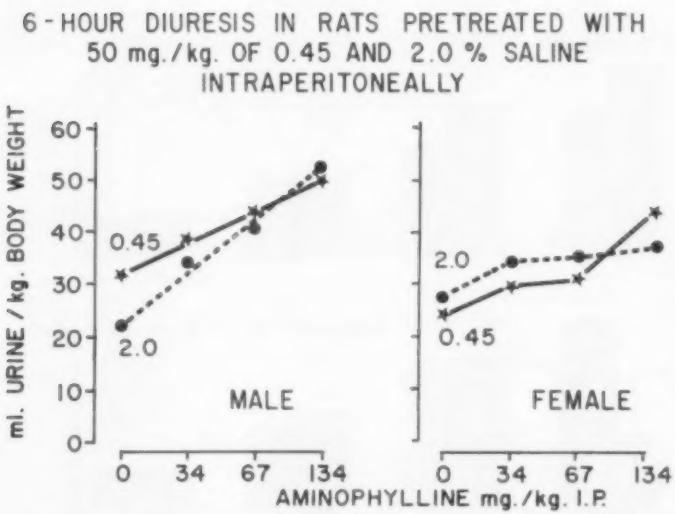
emptied by pulling at the base of the tail. The log dose and log-to-log response curves could then be drawn from the information on water diuresis and for salts, urea, and sodium nitrate. For mercurial diuretics, one can obtain parallel dose-response curves. For xanthine diuretics, the curves were anomalous in that at higher doses there was a fall-off in diuretic action. This has been recently confirmed (13, 14).

From Figure 2, one can see that information in the rat, as gained by the method of Lipschitz, parallels qualitatively the experience obtained with these various categories of diuretics in man. The relative activity of various diuretics is compared to urea in man and rat. Caffeine-type compounds and mercurials are seen to be less active in rats. The relative potencies of the various xanthines in the rat are in agreement with those obtained in rabbits.

FIG. 3.*



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A modification of Lipschitz' oral procedure has been proposed by McColl (15) who set up experiments with controls and three doses of drugs and, a week later, performed the experiment on the same groups of rats, altering the dose pattern according to a Latin square design. The animals in this case were not fasted; they were injected intraperitoneally with 50 ml./Kg. body weight of saline, or saline plus drug. With saline loading, a greater urine flow was obtained which was more conveniently collected.

Figure 3 shows McColl's results using two concentrations of saline injected in male and female rats. With increasing doses of aminophyllin, injected in either 0.45% or 2.0% saline, a linear dose-response relationship was obtained in male rats. Female rats were not suitable subjects, and this has been confirmed by other workers. Figure 4 compares the activity of aminophyllin and acetazolamide by McColl's procedure. A dose-response relationship is seen which is not borne out clinically as far as acetazolamide is concerned. It was not possible to administer organo-mercurials intraperitoneally, but McColl found that intramuscular injection of the mercurials could be used.

Rat techniques can be refined by careful attention to such factors as temperature, randomization of dosages, randomization within the

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FIG. 4.*

COMPARISON OF DIURETIC RESPONSE IN MALE RATS PRETREATED WITH 50 mg./kg. OF .45% SALINE INTRAPERITONEALLY

	I.P. Dose mg./kg.	*6 hr. Urine Output, mg./kg. in Excess of Control*
Aminophylline	34	6
	67	15
	134	18
Acetazolamide	7	15
	14	22
	28	49

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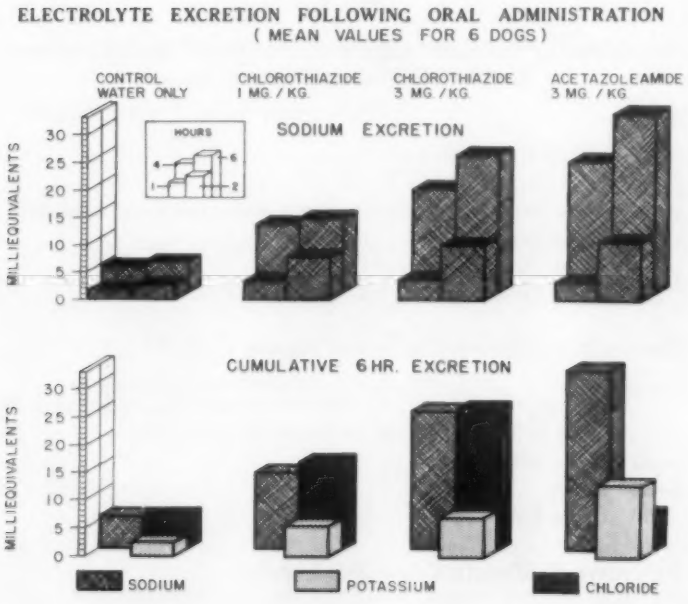
cage, and the amount of light that is present in the room. There is definitely a diurnal cycle in the rat that must be taken into account if one is studying these factors on a 24 hour basis. The age of the rats is important and marked variations result as the rats get older (9). A cage for preventing the contamination of urine by food has been devised (13).

The steady state that is theoretically so desirable to the study of diuretic agents could be achieved by a device (16) in which water or aqueous solution was infused through an indwelling cannula through the cheek of the rat into the stomach. It was possible under these conditions to infuse saline or other solutions, including canned milk, over a period of as long as three days at rates of from 0.1 to 1.0 ml./Kg. per minute. At the end of five hours, a steady state was

FIG. 5.



approximately reached. By means of a device whereby the weight of the animal was continuously recorded on a kymograph, it was noted that as much as 3 ml. of a 5 ml. load was lost insensibly and not excreted.

The use of dogs for oral studies on diuretics was considered in a recent paper by Rosen (17). Urine was collected at intervals over a five-hour period from saline-loaded dogs anesthetized with pentobarbital. A control experiment was done on a series of dogs one week later. The drug was given in a capsule. Each dog served as his own control, and the relative increase in urine volume was calculated. A value for V_t-V_c/V_c greater than 2 indicated an active agent. Data were presented in the paper to substantiate this method of testing for potential diuretic activity in man.

Our oral protocol has been to give 500 ml. of water to trained unanesthetized dogs that have been fasted overnight, and one and one-

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FIG. 6.

EVALUATION OF DIURETIC AGENTS—INTRAVENOUS ADMINISTRATION IN TRAINED UNANESTHETIZED DOGS

Minutes

—90	500 ml. WATER P. O.
—30	3.0 g. CREATININE S. C.
	Begin ISOTONIC MANNITOL-PHOSPHATE, pH 7.4 at 3 ml./min.
0	Urine Discard
5	Blood (femoral venous)
10	Urine Collected, 15.0 ml. Washout of Bladder

REPLICATE 10-MINUTE CLEARANCE PERIODS

	2.5 mg./kg. Drug I. V. Priming Dose. Begin Infusion of Drug at 3.0 mg./kg./hr. in Buffer at 3 ml./min.
+20	Urine Discard
+25	Blood
+30	Urine Collected

REPLICATE 10-MINUTE CLEARANCE PERIODS

half hours later to give a drug by capsule and to collect the urine at intervals of one, two, four, and six hours by catheter so that one can get a measure of the rate at which the diuretic agent takes effect within the six-hour period as well as the total six-hour excretion.

Figure 5 shows the result of this protocol for chlorothiazide and for acetazolamide. At the top is a diagram of cumulative excretion of sodium at one, two, four, and six hours for two doses of chlorothiazide and at the higher dose of acetazolamide. Although the one, two, and four-hour sodium excretions are similar for the two drugs, there is a greater four to six-hour excretion with acetazolamide, suggesting that this agent has a longer duration of action. At the bottom of the figure are shown the relative amounts of sodium, potassium, and chloride excreted by chlorothiazide and acetazolamide. It is apparent that, with acetazolamide, the sodium excretion is not accompanied by

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FIG. 7.*

THEOPHYLLINE-ETHYLENEDIAMINE EFFECT ON WATER AND ELECTROLYTE EXCRETION

Dog 601; Wt. 16.0 Kg.; Exp. 7190

	H_2O		Sodium		Potassium	Chloride	
GFR ml./min.	*UV ml./min.*	*% Reab-sorbed*	*UV μ eq./min.*	*% Reab-sorbed*	*UV μ eq./min.*	*UV μ eq./min.*	*Urine pH*
Control Phase: 500 ml. H_2O—95 Min., 500 ml. H_2O—35 Min.							
44.4	5.5	87.6	59	99.2	50	12	7.1
44.6	5.5	87.7	67	99.1	34	11	7.1
45.0	5.8	87.2	78	98.9	31	16	7.1
† Theophylline-Ethylenediamine: Prime 25 mg./Kg., I. V., Maintenance 30 mg./Kg./Hr., I. V.							
62.8	7.7	87.7	678	95.4	64	530	7.3
55.6	5.0	91.0	437	95.2	48	218	7.4
39.7	3.5	91.2	224	96.5	36	170	7.4

† Total Dose = 933 Mg.

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chloride. Excretion of the bicarbonate anion leads inevitably to metabolic acidosis.

Figure 6 shows the protocol that we have adopted generally for investigation of our compounds by the intravenous route in dogs. This is a renal clearance type of experiment in which the fasted, trained, unanesthetized, female mongrel dog is brought to a state of hydration. Creatinine is administered subcutaneously so that an exogenous creatinine-blood level will remain at about 20 mg./100 ml. throughout the experiment. Creatinine administration is repeated as necessary. A solution which is calculated to be approximately that required to maintain the sodium and potassium balance during the experiment (phosphate buffered at pH 7.4, made isotonic with mannitol) is infused at a rate (3 ml./min.) which permits adequate urine flow. After the creatinine blood level has been attained and the infusion has been carried on for some thirty minutes, the urine in the bladder is discarded and a ten-minute clearance period is begun. At

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FIG. 8.*

AMINOMETRADINE EFFECT ON ELECTROLYTE AND WATER EXCRETION

Control	*Na*		*K*	*Cl*	*Urinary*		*GFR*
Drug	*UV*	*%*	*UV*	*UV*		*Flow*	
Phase	*μ eq./min.*	*Reabs.*	*μ eq./min.*	*μ eq./min.*	*pH*	*ml./min.*	*ml./min.*
Dog 751; Exp. 3155; Drug Dosage 6.25 mg./kg. I. V. Prime, 7.5 mg./kg./hr. by Venoclysis							
C	33	99.5	14	22	5.47	7.0	49.8
D	66	99.0	6	33	5.76	7.0	50.2
Dog 784; Exp. 3185; Drug Dosage 25 mg./kg. I. V. Prime, 30 mg./kg./hr. by Venoclysis							
C	52	99.2	22	15	6.45	6.4	46.5
D	72	98.9	15	28	6.48	2.6	46.4

All values are averages of triplicate successive 10-minute clearance periods.

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the midpoint of this period, a blood sample is collected for calculation of glomerular filtration rate based on exogenous creatinine clearance. At the end of the ten-minute period, the urine is removed from the bladder by an indwelling catheter, a 15 ml. portion of water is added and washed out. These collections are repeated as desirable, for either two or three periods, at the end of which time a drug is given. We have chosen a convenient dose which, when infused at the specified rate, will maintain the blood level of the compound at a more or less constant quantity. In renal clearance experiments, the blood

FIG. 9.

EFFECT OF INTRAVENOUSLY ADMINISTERED CHLOROTHIAZIDE, ACETAZOLAMIDE, AND MERALLURIDE ON THE EXCRETION OF ELECTROLYTES BY DOGS

	Sodium		*Potassium*	*Chloride*	
	μ eq./min.	*% Reabsorbed*	*μ eq./min.*	*μ eq./min.*	*Urine pH*
Chlorothiazide—Dog 802; Exp. 5116; 1.25 mg./kg. I. V. Prime; 1.5 mg./kg./hr. Inf.					
Control Phase [1]	15	99.8	18	9	7.7
Drug Phase	230	96.8	43	171	7.1
Acetazolamide—Dog 810; Exp. 536; 1.25 mg./kg. I. V. Prime; 1.5 mg./kg./hr. Inf.					
Control Phase [1]	15	99.9	16	6	6.0
Drug Phase	125	98.4	78	11	7.9
Meralluride—Dog 758; Exp. 127; 1.25 mg./kg. I. V. Prime; 1.25 mg./kg./hr. Infusion					
Control Phase [1-2]	15	99.8	17	6	6.2
Drug Phase	46	99.4	16	9	6.9
Maximal Effect	213	95.1	36	125	7.2

[1] Av. of duplicate 10-min. clearance values before (control phase) and 20-40 min. after priming dose.

[2] As for 1, except additional clearances performed periodically until maximal effect 80-100 min. after priming dose.

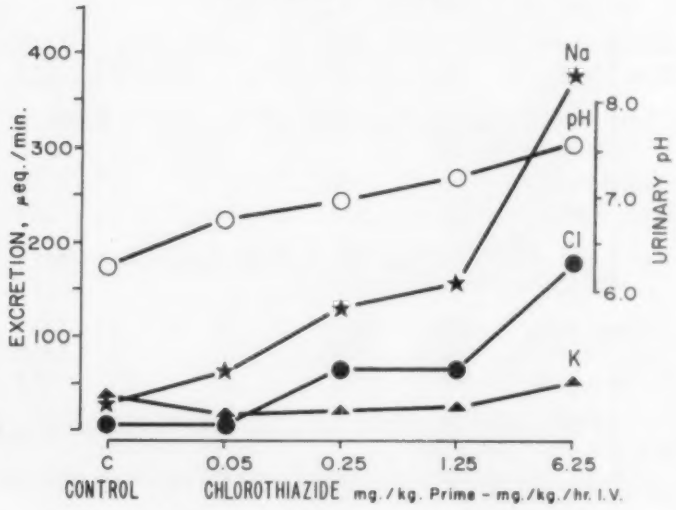
level of an agent must be fairly constant throughout the collection period in order for the calculations to be most nearly true. After allowing some 20 minutes for equilibration of the potential diuretic in body fluids, replicate clearance periods are again taken; the blood and urine are analyzed as appropriate; and calculations of clearances of sodium, potassium, water, and filtration rate are made.

As an illustration of the kind of information that one can collect from an experiment of this type, I have tabulated a series of experiments which illustrate this protocol for some of the categories of diuretics that we have studied.

With mannitol, the excretion of water per minute is increased tremendously; i.e., reabsorption of the water load by the kidney is decreased. Concurrently at this dosage, there is no noticeable increase in the rate of excretion of sodium or potassium.

FIG. 10.

EFFECT OF INCREASING DOSES OF CHLOROTHIAZIDE ON THE pH OF THE URINE AND THE URINARY EXCRETION OF SODIUM, POTASSIUM, AND CHLORIDE IN THE DOG.



Aminophyllin produced a slight increase in filtration rate in this experiment but the water clearance was not appreciably altered (Fig. 7). There is a marked increase in the excretion of sodium and chloride ions. The increase in filtration rate causes a larger electrolyte load to be filtered but, more importantly, a larger fraction of the filtered load escapes reabsorption, as is seen by the decreased reabsorption of sodium in the presence of aminophyllin.

Aminometradine is a very weak agent (Fig. 8). There is an indication here of a small sodium diuresis, a slight decrease in the per cent of the filtered load that is reabsorbed.

A comparison of three different agents—chlorothiazide, acetazolamide, and meralluride is presented in Figure 9. With meralluride, the protocol is necessarily modified because this agent has a delayed onset of action. Ultimately, the increase in sodium excretion, or the depres-

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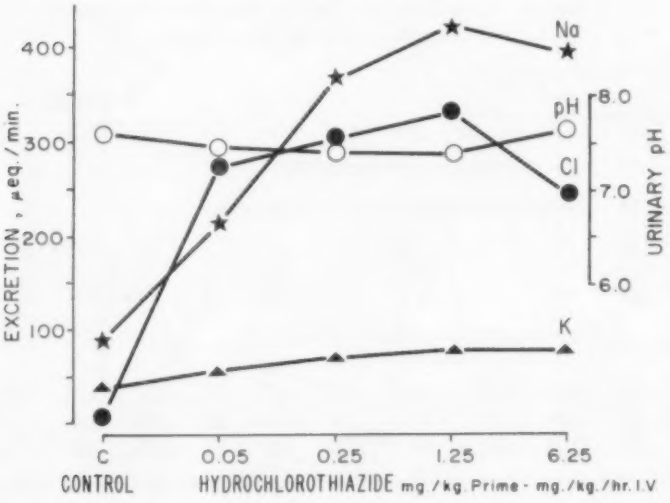
FIG. 11.

EFFECT OF INCREASING DOSES OF HYDROCHLOROTHIAZIDE ON THE pH OF THE URINE AND THE URINARY EXCRETION OF SODIUM, POTASSIUM, AND CHLORIDE IN THE DOG.



sion of sodium reabsorption, is not too different from that seen with the other two agents. The increase of chloride excretion with meralluride is more nearly like that seen with chlorothiazide and quite unlike that observed with acetazolamide.

The protocol can be modified by giving a series of doses of increasing magnitude in a single experiment on a single animal (Fig. 10). The sodium excretion measured here, with increasing doses of chlorothiazide, gives what could be described as a dose-response effect. As a single experiment in a single animal, this is not subject to dose-response statistics, but an experiment of this kind is helpful to show the relative potency of two compounds (compare Figs. 10 and 11). Thus, by contrast with the two lowest doses of hydrochlorothiazide (Hydrodiuril ®), there is a greater sodium and chloride excretion than with chlorothiazide. At the lowest dose, hydrochlorothiazide is active where chlorothiazide showed little or no activity.

A few words could be added with regard to various other traits of compounds which are important in their over-all evaluation: there

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FIG. 12.*

RENAL CLEARANCE OF CHLOROTHIAZIDE EXCEEDS GLOMERULAR FILTRATION RATE

	Chlorothiazide								
	Plasma	*Clear-*			*μ eq./min.*			*Urine*	
Time min.	*Conc. mg./L.*	*ance ml./min.*	*GFR*	*C.R.*	*Na+*	*K+*	*Cl−*	*ml./min.*	*pH*
— 30	3 gm. Creatinine subcutaneously								
— 20	Mannitol-Phosphate at 3 ml./min.								
20			46.8		85	7	14	2.8	7.01
30			49.1		82	7	12	3.5	6.90
40			37.7		70	8	11	3.7	6.82
	Chlorothiazide: 12.5 mg./kg. Prime I. V. 15.0 mg./kg./hr.								
70	34.8	135	39.8	3.4	443	71	272	3.3	7.71
80	32.0	149	43.7	3.4	526	69	308	4.0	7.67
90	29.2	122	33.5	3.6	389	51	256	3.0	7.40

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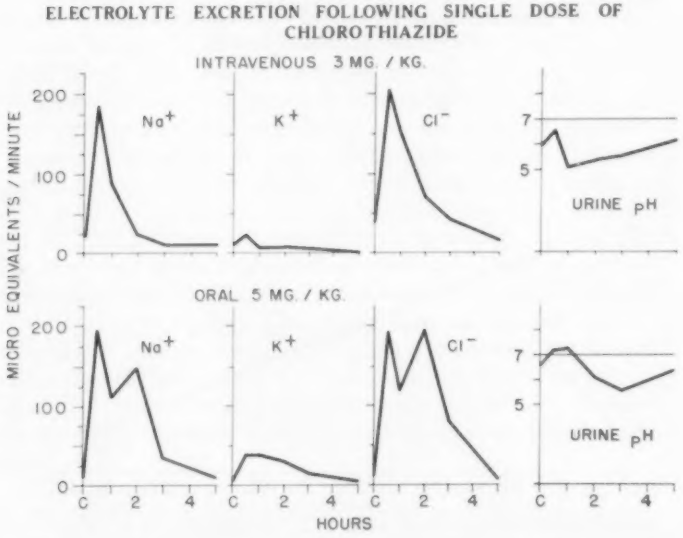
is, as was indicated previously, the fate of the compound itself, the completeness with which it is absorbed, the rate at which it is excreted, the rate at which it is distributed into various tissues, and the extent or the rate at which it is degraded. Some of these characteristics can be illustrated by reference to chlorothiazide. If one measures the plasma concentration and urinary excretion of chlorothiazide, it is found that it is excreted at some two and one-half times the glomerular filtration rate (Fig. 12). This indicates the participation of the renal tubules in the excretion of the drug and suggests that the drug will be excreted fairly rapidly and, furthermore, that the compound will be present in a high concentration at its site of action in the renal tubules.

One can modify the type of experiment we have been discussing by giving a single dose of the drug either orally or intravenously and following the excretion of sodium and chloride for several hours. After either route of administration, the onset is fairly rapid and the actual

FIG. 13.*



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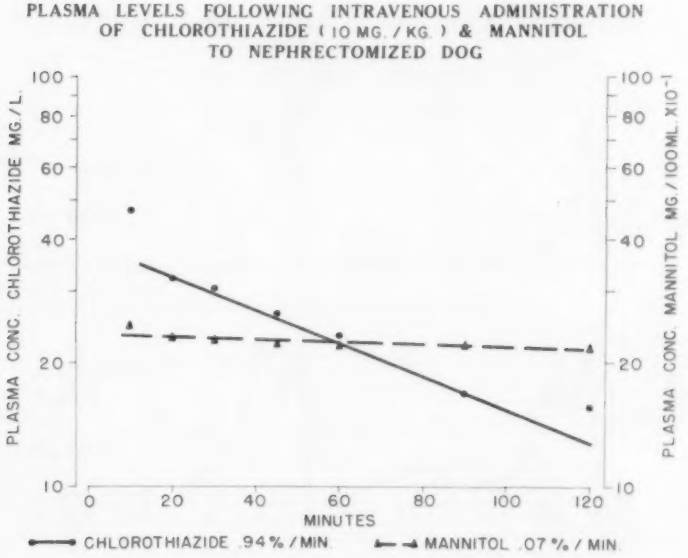
excretion is almost the same, suggesting that the absorption of the drug is rapid and essentially complete (Fig. 13).

One can gain some insight into other factors of degradation and distribution through the tissues by the device of using nephrectomized animals to minimize excretion of the drug. Taking as a base line mannitol (which will persist in the blood for a number of hours in the absence of functional kidneys but which is excreted very rapidly by the kidneys), one finds that the level of chlorothiazide falls slowly even in a nephrectomized animal (Fig. 14). For purposes of drug evaluation, the experiment shows clearly that there are sources other than renal which participate in the dissemination or metabolism of the drug. A discussion of the fate of chlorothiazide, its excretion in the bile and apparent lack of metabolism, is beyond the scope of this paper.

Together with information on potency and spectrum of action, these facts permit the selection of the most promising diuretic agent.

FIG. 14.*



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Part II

By Karl H. Beyer

I think that, in the evaluation of diuretic agents over the course of time and historically, you have a situation which would be very similar to trying to develop a new chemotherapeutic agent without making use of a background of knowledge of bacteriology. This would be like trying to develop an agent for the treatment of pneumonia without knowing necessarily what causes pneumonia.

Oversimplified, older diuretic assays required only that you put some water in a rat that had been taken off water for a while and then measure how much came out. This is something like trying to develop an agent for pneumonia by leaving rats in a cold room for a while and hoping that they would get pneumonia. Then, you would administer your compound and see whether or not the sick rat lived.

Actually, in the evaluation of diuretic agents, one is dealing with an exercise in electrolyte and water physiology. In this instance, emphasis is placed on the effect of the kidney in modulating electrolyte and water balance. Clinically, one usually deals with an accumulation of fluid which is not due to an excess of water imbibed, but to a decrease in the amount of electrolyte excreted per unit of time.

A decrease in electrolyte excretion may be due to an impairment in glomerular filtration. In such a circumstance, the percentage reabsorbed of that electrolyte which is filtered is sufficient to yield a net gain in sodium chloride to the animal, and so a secondary retention of water and a building-up of extracellular fluid results. On the other hand, there may be no impairment of glomerular filtration rate and, yet, a real increase in renal tubular reabsorption of sodium chloride, as in the iatrogenic edema induced by some of the corticosteroids employed for the treatment of arthritis. Hyperaldosteronism is another example where there is a real increase in the reabsorption of sodium by the renal tubules and some accumulation of fluid. Interestingly enough, in the latter instance, there is not a marked attendant edema.

Thus, all one tries to do with a diuretic agent is to bring back into balance the glomerular filtration and the renal tubular reabsorption of salt and, secondarily, of water. The problem is this simple from the physiologic standpoint. One has either to increase the

glomerular filtration rate—xanthines do this, but not very effectively—or one has to decrease the renal tubular reabsorption of sodium, preferably as sodium chloride.

If one is interested primarily in the balance between glomerular filtration and tubular reabsorption of salt, then it makes very good sense to design the experimental method to measure this relationship. Let's weigh the advantages of rats and dogs for this type of assay purpose. The rat has advantages in that it is a small animal adaptable to protocols where results may be analyzed statistically. The rat does not require very much compound and this holds a certain charm for the organic chemist who may be supplying compounds for the assay.

On the other hand, the rat assay does not lend itself to precise analysis of glomerular filtration or tubular reabsorption of water and electrolytes which is so essential to a precise interpretation of the action of a potential diuretic agent. The reasons for this are strictly technical.

In the dog, it is technically possible to measure rather precisely glomerular filtration rate, tubular reabsorption, and tubular secretion. This permits a fine discrimination of a potential diuretic agent. To be sure, one needs more compound for a given experiment in the dog. On the other hand, as may be observed from the design of the protocols that Dr. Baer described, one can design the experiment so that one has an internal audit—the control and the drug phase within the same experiment. You do not need statistics to do renal clearance work in the dog. One technically good experiment is just about as good as the next good experiment and statistical methods are really not necessary for interpretation of results.

These several classes of compounds mentioned by Dr. Baer also hold a story with respect to the practical aspects of drug evaluation. The xanthines, as has been indicated, are effective saluretic agents—that is, they cause sodium and chloride to be excreted predominantly. These would be suitable compounds if they worked when you wanted them to, but they are most effective when you need them least. That is to say, they are not sufficiently potent compounds for the management of edema accompanying cardiac decompensation.

The aminouracil type of compound is more effective than the xanthines. One can employ these agents for the maintenance of therapy once one has brought the patient clinically into adequate

water balance with a more potent agent, as with an organo-mercurial diuretic. They are useful and, in some patients, one can do the whole job with these agents. They have commanded attention in the last few years.

The organo-mercurials have been the mainstay of therapy in the diuretic field for many, many years, and they are very useful agents. The only trouble with the organo-mercurials is that they must be given parenterally to be really reliable. They are not commonly employed intravenously. Intramuscular administration is perfectly safe and some of these drugs produce very little irritation when administered in this manner. The organo-mercurials cause an undesirably high incidence of gastrointestinal distress when administered orally.

More recently, a class of compounds of which chlorothiazide is the prototype has given rise to the most important diuretic agents in the sense that they are well-absorbed, well-tolerated on oral administration, and induce predominantly a saluretic effect. Factors of real consequence in the evaluation of these agents have to do with things other than potency, although they incorporate this attribute as well.

Dr. Baer mentioned *in vitro* versus *in vivo* evaluation of these compounds. For example, in the carbonic anhydrase inhibitors, there is no real parallelism between the *in vitro* potency of these compounds and their *in vivo* utility as saluretic agents. This is true even in a qualitative sense for, in some instances, predominantly bicarbonate whereas, in other instances, predominantly chloride is excreted as the anion. But, never forget that, in trying to correlate an *in vitro* with an *in vivo* effect, one compares data from an oversimplified model system with an effect in not an organ but the whole organism. Thus, in the latter instance, one deals not only with the effect of the compound on the body but the effect of the body on the compound. For example, in a carbonic anhydrase inhibitor designed for a renotropic effect, one is particularly interested in limiting the distribution of the compound to only that part of the carbonic anhydrase system contained in the nephron.

This same hazard of correlating *in vitro* with *in vivo* effects of the organo-mercurials obtains, for almost any organo-mercurial will inhibit *in vitro* sulfhydryl catalyzed systems. However, there is almost no correlation between the *in vitro* potency and the *in vivo* action of these agents which undoubtedly work through inhibiting some sulfhydryl-catalyzed system.

In closing, I would say that, in the evaluation of diuretic agents, like any other exercise in pharmacology, one should design his assay just as close to the basic physiological problem involved as it is possible to do. This is not peculiar to renal physiology. It is axiomatic to the evaluation of compounds generally. The evaluation of diuretic agents is certainly no exception.

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A DECADE OF CHEMOTHERAPEUTIC MANAGEMENT OF HODGKIN'S DISEASE

By John R. Sampey *

IRRADIATION and nitrogen mustard therapy have been the most frequently employed methods within the past decade in the management of Hodgkin's Disease (2, 8, 9, 12, 16, 17, 18, 19). In tabulating 6869 cases treated with a dozen chemotherapeutic agents, nitrogen mustards were used in over 60 per cent of the cases. In other reviews, Marlow (12) preferred x-rays to mustards, while Brimi (2) and Wintrobe *et al.* (22) rated the two of equal value, and Larenov and Ziv (9) concluded chemotherapy was better than irradiation. Diamond (3), Rottino (16), etc., recommended a combination of x-rays with nitrogen mustards or triethylene melamine.

Triethylene melamine is the second most frequently used chemical in Table I in the control of Hodgkin's Disease, and it has a higher remission rate than nitrogen mustard therapy. Remission rates were calculated from reports which indicated both the number of patients treated and the number responding. Scores of clinical reports in the literature fail to give these data essential to a numerical evaluation of the therapy. The data on nitrogen mustards were calculated from 278 published reports, and those on triethylene melamine from 89 references. Hettig (6) reported 77 per cent of 151 patients showed improvement on nitrogen mustards. Bernard (1), Diamond (3, 4), MacDonald and Yettra (11), and Schulten and Pribilla (21) all rate triethylene melamine highly in their review of the literature. Karnofsky (7) and Paterson (15) judge HN2 as the agent of choice in early or acute stages of Hodgkin's Disease, while triethylene melamine is preferred in the later stages. Farber (5) has stressed the need for more alkylating agents, and Larionov (10) has stated that the action of these drugs is more than palliative today.

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TABLE I

CHEMOTHERAPEUTIC MANAGEMENT OF 6869 CASES OF HODGKIN'S DISEASE

Chemicals	*Total No. of Cases*	*No. Not Evaluated*	*Good Rems.*	*Fair Rems.*	*Rem. Rate*	*No. of Refs.*
Nitrogen mustards	4246	1482	817	922	63%	278
Triethylene melamine	925	127	198	368	70%	89
Antibiotics	794	103	69	249	46%	64
ACTH, adrenal steroids	312	18	39	196	80%	59
Colchicines	152	38	40	50	78%	28
Phosphoramides	83	—	18	34	63%	18
Myleran	82	10	18	34	72%	11
Phenylbutazone	74	—	18	33	70%	8
Folic acid antagonists	68	—	4	35	57%	13
Ethyleneimines	49	—	10	14	49%	13
Radiophosphorus	48	—	11	12	48%	16
Urethan	36	24	—	7	58%	7

Antibiotics are the third most frequently used chemicals in Table I but their evaluation is complicated by the fact that they are often used as supportive therapy with other cancerostatic agents (19). Murphy has recently recommended their use in early stages of Hodgkin's disease (14).

ACTH and adrenal steroids show the highest remission rate of any agent in the series, but the ratio of good to fair remissions is not impressive. In the evaluation of these two types of responses, three factors have been taken into consideration; namely: (1) the amelioration or complete absence of clinical evidences of the disease; (2) the effect of the drug on the blood picture; (3) and the duration of the response.

Colchicines also show a high rate of remission, and the ratio of good to fair response is fair, but these drugs are not ranked high in other reviews of Hodgkin's disease (7, 13, 21).

Myleran, phenylbutazone, and phosphoramides have the highest remission rates of the remaining agents in Table I, but the number of patients treated is limited. Several miscellaneous agents reported in an earlier study (18) show some promise of larger usefulness in the chemotherapeutic management of Hodgkin's disease.

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SELECTED ABSTRACTS

The Effectiveness of Amphotericin B as an Antifungal Agent in Conjunction With Tetracycline. Stough, A. R., Groel, J. T., and Kroeger, W. H. *Antibiot. Med. & Clin. Ther. 6*:653 (1959). The overgrowth of *Candida albicans* in the intestinal tract during therapy with tetracycline has been given considerable attention. Nystatin has gained acceptance as an antifungal agent in conjunction with tetracycline therapy, but its extremely bitter taste and limited aqueous stability has limited its usefulness. Amphotericin B has been found to have antifungal activity and to be practically tasteless, as well as stable in aqueous media. Consequently, the authors studied the potential value of combining amphotericin with tetracycline.

In all, 128 adult healthy subjects were used in several studies. In the first study, 250 mg. tetracycline phosphate complex capsules were given to all subjects 4 times a day for 7 days. Subsequently, tetracycline was continued at the same dosage level for an additional 7 days and amphotericin B was given concurrently at dosage ratios of 2.5:1 to 20:1. After six days, the average per cent reduction of *C. albicans* colonies in the stool specimens varied from 65 per cent to 99 per cent for the dosage ratios employed, with no significant relationship between the dosage of amphotericin and the percentage reduction. The authors selected the 5:1 ratio for further study and confirmed its effectiveness. In other studies with this ratio, it was found that amphotericin B did not interfere with the absorption of tetracycline, for serum levels were obtained comparable to those obtained without the presence of amphotericin B. It was also found that there was little or no intestinal absorption of amphotericin, for no detectable serum levels of this compound were found.

No evidence of systemic toxicity or complaints of gastrointestinal disturbances were noted in any of the subjects.

The authors concluded that amphotericin B may be combined with tetracycline in a ratio of 1:5 as a safe and effective antifungal agent to prevent the overgrowth of *C. albicans* in patients receiving extended therapy with tetracycline. In addition, amphotericin B is tasteless and stable in aqueous media and, thus, lends itself to formulation into aqueous suspensions in combination with tetracycline.

The Formulation of Coal Tar Ointments. Lloyd, W. R., and King, J. C. *Amer. Perfumer 73:37* (Sept. 1959). The authors discussed the development of coal tar ointments through the records of history and then dealt in some detail with more recent formulation developments.

Experimentally, the authors studied the effects of various emulsifiers on a modified hydrophilic ointment and a washable ointment base containing several solid and liquid oil-phase ingredients. The coal tar fraction used was obtained from the alcohol soluble portion of coal tar solution and designated coal tar oil. The authors evaluated the cosmetic acceptability, the consistency, and the release of medicament. Cosmetic acceptability was a subjective evaluation performed by the authors. The consistency was evaluated by means of the depth of penetration of a 5 Gm. steel bar into the ointment from a constant height and was of comparative value only. *In vitro* release of the coal tar fraction was measured by the inhibition of *Trichophyton mentagrophytes* (ATC 9129).

The following formula was developed as a washable coal tar and zinc oxide ointment being light yellow in color, comparatively nonstaining, and having a pleasant texture. Inhibition zones compared favorably with a similar ointment having as its base Hydrophilic Ointment U. S. P. XV.

Zinc Oxide	150 Gm.
Starch	150 Gm.
White Petrolatum	320 Gm.
Polyoxethylene Sorbitan Monolaurate	40 Gm.
Coal Tar Oil	20 ml.
Propylene Glycol	120 ml.
Stearyl Alcohol	6 Gm.
Purified Water	140 ml.
To make about	1000 Gm.

The starch and zinc oxide are added to the melted stearyl alcohol and white petrolatum and stirred until smooth. The polyoxyethylene sorbitan monolaurate and propylene glycol are dispersed in the water. Both mixtures are heated to 70° C.; the aqueous solution is added to the oleaginous and they are stirred until nearly congealed. The coal tar oil is added and the mixture stirred until homogeneous.

Treatment of Pediatric Infections With Triacetyloleandomycin. Ripberger, F. M., Jr., Anderson, R. H., and Palmer, R. E. *Antibiot. Med. & Clin. Ther. 6:662* (1959). Triacetyloleandomycin, as compared with oleandomycin, has been shown to provide more complete systemic absorption with consequently higher and more rapid blood concentrations and less gastrointestinal intolerance. In addition, it is practically tasteless and poorly soluble in distilled water, but is readily soluble in acid solutions, such as gastric juice.

The authors undertook a study of the effectiveness of triacetyloleandomycin in the treatment of 200 private practice pediatric patients, 182 of whom were suffering from respiratory infections and 15, with soft-tissue infections. The dosage employed ranged from 125 mg. a day for small infants to 1.5 Gm. a day for a few adult patients included in the study. An oral suspension was used for younger patients and capsules for those who were older. Therapy was continued for a period of from 3 to 10 days in most of the patients. One infant received treatment, with an eventual cure, for 34 days.

Cultures were obtained from all patients before therapy was started. In 35 per cent of the cases, organisms were found that were resistant to triacetyloleandomycin. Seventy-two per cent of all cultures were of single organisms, the majority of which were streptococci and staphylococci.

Following a single course of therapy, 85 per cent of all patients were cured, and 9.5 per cent were improved. In most of the patients in whom cures were achieved, marked improvement was evident within 24 to 48 hours.

Repeat cultures were carried out in 73 patients between 3 and 30 days after the first culture. In 37 (50 per cent), organisms were found that were resistant to triacetyloleandomycin, either the original infective organism or other resistant strains. However, in 29 of these 37 patients in whom resistant bacteria had persisted, a clinical cure had been achieved with improvement in 4 others. This finding caused the authors to conclude that the bacterial susceptibility test cannot be considered an infallible guide to treatment.

In only 6 per cent of the patients treated were there mild side effects consisting of looseness of the stool.

A Study of the Response of Diabetics to Tolbutamide Therapy. DeLawter, D. E., Moss, J. M., Tyroler, S., and Canary, J. J. *J. A. M. A. 171:*1786 (1959). A group of 200 nonketotic patients with diabetes mellitus were observed for several months up to a period of three years with regard to their response to continued therapy with tolbutamide. Those patients who obtained a statisfactory response were maintained on an average dose of 1 Gm. per day. The dose was raised to a maximum of 3 Gm. per day before the drug was considered to have become ineffective. Patients were considered to have excellent control if their fasting blood sugar levels ranged from 100-160 mg. per 100 ml. (Folin Wu Method).

Thirty-two patients were classified as primary failures because they did not respond to therapy with tolbutamide from the beginning. Cases in which the patient gradually became unresponsive were classified as secondary failures. Secondary failures occurred during the course of the study at the rate of about 3 per cent of the patients treated per month. The authors stated that it appeared likely that all patients would eventually become resistant to the hypoglycemic effects of tolbutamide. It was found that patients with poor initial diabetic control developed secondary failure sooner than those with good initial control. When it was necessary to re-institute insulin therapy, there was no significant change in the insulin requirements after tolbutamide therapy as compared with prior to the use of tolbutamide.

Once a patient failed to respond to therapy with tolbutamide, the failure was permanent. However, some of the patients who exhibited primary or secondary failures with tolbutamide responded to treatment with chlorpropamide, metahexamide, or phenethylbiguanide (DBI). About 20 per cent of the patients evaluated responded to treatment with the first two drugs and about 55 per cent to treatment with DBI. However, these cases were not followed for long periods and the final outcome of therapy was not known.

The authors concluded that all mature, nonketotic diabetics whose condition cannot be controlled by diet alone deserve a trial with tolbutamide therapy. Patients who are spared insulin injections for even a few months are grateful for this reprieve; however, all patients on tolbutamide therapy must be followed closely since secondary failures often develop with little warning.

The Effectiveness of a Multiple Antigen for Immunization Against Poliomyelitis, Diphtheria, Pertussis, and Tetanus. Barrett, C. D., Jr., Timm, E. A., Molner, J. G., Wilner, B. I., Fahey, M. F., and McLean, I. W., Jr. *Am. J. Pub. Health 49*:644 (1959). A new multiple antigen containing poliomyelitis vaccine combined with diphtheria and tetanus toxoids and pertussis vaccine was evaluated for antibody formation potential in infants and children. The desirability of using such a combined preparation has been recognized.

A group of 224 infants and children completed their primary series of injections and 104 received booster injections. Children over 6 months of age received 3 monthly injections and those under 6 months of age received 4 monthly injections in the primary series. Booster injections were given about 18 months later.

The fourth dose given to the younger infants greatly improved their seroimmunological response and brought their antibody levels in line with those obtained in older children with only three injections. The booster dose was found to be extraordinarily effective in enhancing the antibody formation. This uniformly high response to the booster dose occurred regardless of the age at which primary immunization was begun and regardless of the antibody level following the primary series. The booster response was found to be a far more meaningful criterion for evaluating the effectiveness of the polio vaccine components than were serum antibody levels after the primary series of injections.

No clinical reactions of any consequence were observed in any of the infants or children in this study.

A Method for the Determination of Low Concentrations of Antibacterials After Contact With Bacteria. Beckett, A. H., Patki, S. J., and Robinson, A. E. *J. Pharm. Pharmacol. 11*:352 (1959). A method is described for the quantitative separation of certain antibacterial agents from bacterial cells and bacterial exudates, thus eliminating interferences for ultra-violet spectrophotometric assay of the agent.

The general procedure was carried out as follows. After bacterial contact with the antibacterial agent, the bacteria were removed by

centrifuging. Twenty-five ml. of the supernatant solution were shaken with portions, usually 25 ml. and 4 × 15 ml., of a water-immiscible solvent. Solvents were selected for suitability in obtaining quantitative separation of the drug from the cell exudate and subsequent preparation of the drug and exudate for spectrophotometric analysis. The solvent layers were combined, washed with water, and evaporated to dryness under reduced pressure. The residue was dissolved in water (using heat if necessary), the solution diluted to 50 ml., and examined spectrophotometrically. Verification studies established that the agent constituted the only ultra-violet absorbing substance in the solution. The combined aqueous layers remaining after the extraction, containing the bacterial cell exudates, were boiled to remove the organic solvent, cooled, diluted to 50 ml., and examined spectrophotometrically.

This simple liquid-liquid extraction procedure was found to effect the desired separation. The selection of solvents was found to be quite important. Hexylresorcinol, chloroxylenol, and oxine were extracted with chloroform, and chloramphenicol was extracted with diethyl ether and ethyl acetate.

The authors concluded that it should now be possible to reappraise the effects of drug concentration on the bactericidal action of phenolic compounds in relation to the amount of drug bound.

BOOK REVIEWS

Subsidia Pharmaceutica 1959. (S. Ph.I 1957 et Supplementa 1958, 1959. Scientific Center of the Swiss Pharmaceutical Society (Wissenschaftliche Zentralstelle des Schweizerischen Apotheker-Vereins). Swiss Pharmaceutical Society (Selbstverlag des Schweizerischen Apotheker-Vereins), Zürich, 1959.

In continuation of their previously stated policy (see book review, this journal March 1958 and May 1959), the editors publish additional information for the benefit of the practicing pharmacist:

a. The Index Nominum is an independent supplement, listing about 1700 of the most important drugs. The arrangement is the same as in the original Index. This supplement is to be filed following the original Index.

b. The monographs on "Pharmaceutical Classification" (Therapeutische Stoffklassen) are supplemented by two chapters: "Parasympathomimetics" and "Parasympatholytics," written by Prof. Dr. J. Büchi. With these additions, the article series dealing with the autonomic nervous system attains a thorough coverage of this important field of pharmacologic action.

c. There is one addition for the chapter on "Assay Methods." It describes the analytical procedures for Tolazoline Hydrochloride.

d. Directions for the preparation of solutions isotonic with blood and tear fluid constitute the last addition to this compendium. This should prove very valuable to the practicing pharmacist. A table and a graph provide the necessary information for quick reference.

With these additions, the *Subsidia* will be of even greater value not only for the busy retail pharmacist but also for the physician, for industrial concerns, and for many others who are interested in the manufacture, distribution, and dispensing of drugs.

ELSA EHRENSTEIN

A Contribution to Western Pennsylvania Pharmacy. Edward C. Reif and Thelma C. Reif. 416 pp. University of Pittsburgh Press, Pittsburgh, Pa. Price: $6.00.

This meticulous history of the School of Pharmacy of the University of Pittsburgh is indeed a history also of pharmacy and medicine in the area surrounding that western Pennsylvania city. From the founding of the school in 1878 as the Pittsburgh College of Pharmacy utilizing space in the Western University of Pennsylvania through the merging of the Scio College of Pharmacy with the Pittsburgh College of Pharmacy and, finally, through the merger of the Pittsburgh College of Pharmacy with the University of Pittsburgh, the pages of this treatise (even the pages are tinctured with pharmaceutical symbols) are replete with historical documents, programs, faculty lists and biographies, pictures and prints, alumni lists, and practically everything that entered into any phase of the progress of this enterprising teaching institution.

The authors and compilers of this painstaking work, the third dean of the College from 1945 to 1958 and his wife, deserve great credit for producing this volume, described so aptly on the book jacket as a labor of love.

JOHN E. KRAMER

Organic Syntheses, Vol. 39. Max Tishler, Editor. vii + 114 pp. John Wiley and Sons, Inc., New York 16, N. Y., 1959. Price: $4.00.

Volume 39 of this annual work is composed in the style characteristic of the previous editions of this extremely useful book. In all, thirty-one rigorously checked syntheses utilizing commonly employed synthetic procedures are given. All types of organic substances from metallo-organic through heterocyclic and polynuclear aromatic compounds are included. The ample (thirty-four page) index is cumulative for volumes 30-39 inclusive. The utility of this series is so well known it would be superfluous and inadequate to add any further plaudits.

A. R. GENNARO

Medieval and Rennaissance Medicine. Benjamin L. Gordon. xii + 843 pp. Philosophical Library, Inc., 15 E. 40th Street, New York 16, N. Y., 1959. Price: $10.00.

References to medicine, medical practices, and medical practitioners in the Middle Ages were scattered and hard to centralize until the advent of this book. Now, the historian, the student, the physician —anyone who has interest—may utilize this volume to determine facts about medicine in those dark ages.

The subject matter is treated in a number of ways, all of them most interesting. The various fields of medicine (and surgery) as then practiced are discussed; medical practices in the parts of the then known world are described; the scope and the influence of institutions of medical learning are outlined; and there are sections dealing with the influence on medicine of the several religions then in vogue. Types of surgery and medication are graphically described, and there are biographical sketches of the physicians, scientists, and any others who, in any way, contributed to the healing arts in the Middle Ages.

A lengthy and detailed reference schedule gives the astute reader many other documents to be used for supplementary reading. An extensive index makes possible quick reference to subject matter.

Historical works have the possibility of becoming dull and boring. Such is decidedly not the case with this work. The author writes well, tells the immediate story under discussion, and goes quickly on to the next point. There is indeed a wealth of data included in these 843 pages, and numerous illustrations help maintain the interest.

JOHN E. KRAMER

Nutrition and Atherosclerosis. L. N Katz, J. Stamler, and R. Pick. 146 pp. Lea & Febiger, Philadelphia, Pa., 1958. Price: $4.50.

This book appears as the culmination of the combined efforts of the authors to present in an abbreviated fashion a review but, at the same time, a comprehensive picture of the present status of research on atherosclerosis. Recognizing the fact only too clearly that atherosclerosis and its associate, hypertension, represent the most important morbidity and mortality producing conditions in the United States

today, these authors have summarized the more outstanding concepts of the research on these conditions in a concise and understandable manner.

The major portions of this book are devoted to the topic of the nutritional aspects of the problem. Epidemiological findings on a world-wide scope are indicated. The role of cholesterol, experimental animal findings, and hormonal and endogenous factors are considered in separate sections. In each case, a brief historical sketch precedes the recent evidence on the subject. In a final chapter, the prophylactic and therapeutic approaches currently in vogue are described.

This is an excellent, easy-to-read and understand coverage of the available information on a complex and important disease condition. It is the type of book that the pharmacist, physician, or business man can appreciate and from which he can gain a conversational knowledge of the atherosclerotic situation from reading. The individual in research at the same time can refer to its bibliography for a ready source of literature pertaining to his investigations.

THOMAS H. F. SMITH

Connective Tissue, Thrombosis and Atherosclerosis. I. H. Page. x + 316 pp. Academic Press, Inc., New York 3, N. Y., 1959. Price: $9.50.

Displaying once again the ingenuity and initiative which have combined to make him one of the most renowned contributors to our knowledge of atherosclerosis, Dr. Page, in this book, offers a unique and unexplored approach to the problem.

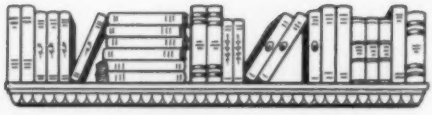
Rather than "just another symposium on atherosclerosis . . .," he pioneered with his efforts by inviting researchers whose primary interests lay in correlated disciplines. His logic concluded that ample investigations of lipids, cholesterol metabolism, blood pressure, and nutritional factors were in progress and sufficient publications on these topics were available. With this meeting and subsequent publication of the book herein described, he has focused attention on additional important concepts and simultaneously initiated a new group of cellular physiologists, biophysical chemists, morphologists, and enzymologists into the field of atherosclerosis research.

The emphasis in this book is placed on the functional problems occurring at the molecular level which approach is, unfortunately, not common enough in today's research.

Intriguing concepts of collagen structure and function and the significance of blood clot formation mechanisms and fibrinolysis as an approach to the pathogenesis of atherosclerosis is considered and elaborated.

Although the title of this book appears formidable and perhaps of relatively minor interest to investigators of atherosclerotic problems, it is an unforgivable mistake for them to neglect to examine the profound information contained within its covers. No scientifically minded individual can read this work and fail to gain some new insight into solving a phase of the profound problem of atherosclerosis now facing mankind.

THOMAS H. F. SMITH



American Journal of Pharmacy

The American Journal of Pharmacy is the oldest continuously published scientific periodical of its kind in America, having been established by the Philadelphia College of Pharmacy in 1825. After the original issue there were three other preliminary numbers until 1829, when regular publication began. From then until 1852 four issues were published annually, with the single exception of 1847, when an additional number appeared. Six issues a year were printed from 1853 to 1870, at which time the Journal became a monthly publication.

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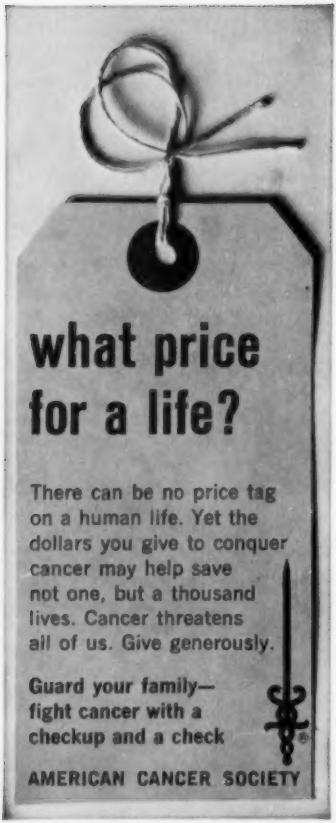
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